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Impact of perinatal COVID on fetal and neonatal brain and neurodevelopmental outcomes

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ABSTRACT

After three years of the COVID-19 pandemic, we have learned many aspects of the disease and the virus: its molecular structure, how it infects human cells, the clinical picture at different ages, potential therapies, and the effectiveness of prophylaxis. Research is currently focused on the short- and long-term consequences of COVID-19. We review the available information on the neurodevelopmental outcome of infants born during the pandemic from infected and non-infected mothers, as well as the neurological impact of neonatal SARS-CoV-2 infection. We also discuss the mechanisms that could potentially affect the fetal or neonatal brain including direct impact after vertical transmission, maternal immune activation with a proinflammatory cytokine storm, and finally the consequences of complications of pregnancy secondary to maternal infection that could affect the fetus. Several follow-up studies have noted a variety of neurodevelopmental sequelae among infants born during the pandemic. There is controversy as to the exact etiopathogenesis of these neurodevelopmental effects: from the infection itself or as a result of parental emotional stress during that period. We summarize case reports of acute neonatal SARS-CoV-2 infections associated with neurological signs and neuroimaging changes. Many infants born during previous pandemics caused by other respiratory viruses demonstrated serious neurodevelopmental and psychological sequelae that were only recognized after several years of follow-up. It is essential to warn health authorities about the need for very long-term continuous follow up of infants born during the SARS-CoV-2 pandemic for early detection and treatment that could help mitigate the neurodevelopmental consequences of perinatal COVID-19.

1. Introduction

Since the declaration of a pandemic caused by SARS-CoV-2 in March 2020 by the World Health Organization (WHO) [1], researchers from all over the world recognized the need for learning more about this virus. The mechanisms of infection, the various clinical presentations, potential therapies, and the ways of preventing it were the core of these investigations.

Currently, many scientists are focused on the detection of potential short- and long-term sequelae after exposure to SARS-CoV-2. For obstetricians, neonatologists and health care personnel working in perinatal medicine the potential sequelae of maternal and neonatal infection on later infant development are unclear. Furthermore, even without an infection being detected, the pandemic itself could affect pregnant women and impact the long term development of their offspring.

SARS-CoV-2 preferentially binds to the angiotensin-converting enzyme (ACE2) and its expression was easily detected in multiple brain regions [2]. Therefore, the potential exists for neurodevelopmental impairment to occur after fetal, neonatal, and young infant infection.

Moreover, any possible sequelae of COVID-19 during pregnancy should be of concern, even if mild, given the large number of affected pregnant women during the pandemic [3].

In this review we will summarize the available information on the possible neurodevelopmental sequelae of infants born during the SARS-CoV-2 pandemic.

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1.1. Potential mechanisms of the effects of SARS-CoV-2 on infant development (Fig. 1.)

1.1.1. Vertical transplacental transmission and direct impact on the central nervous system

There is evidence that some viruses, such as Zika and Cytomegalovirus, can cross the placenta and invade the blood brain barrier with devastating effects on the infants' brain [4,5] The possibility and potential frequency of vertical transmission of SARS-CoV-2 are a matter of current debate and addressed in another manuscript in this issue. There is no clear description of how vertical transmission should be defined.

The WHO defines vertical transmission by the presence of maternal infection during pregnancy, detection of SARS-CoV-2 or persistence of an immune response in the newborn [6]. Shah et al. proposed that, to confirm vertical transmission, transplacental infection can only be established with virus detection by PCR in umbilical cord blood or neonatal blood collected within the first 12 h of birth, or amniotic fluid collected before rupture of membranes [7]. Blumberg et al. propose that mothers have to be positive for SARS-CoV-2 from 2 weeks before to 2 days after delivery for perinatal transmission. Maternal infection can theoretically occur anytime during pregnancy for potential vertical transmission. In addition, one of the following is mandatory: a positive nasopharyngeal, oropharyngeal or saliva swab from the newborn within the first day, or a positive sample from amniotic fluid or neonatal blood before 24 h. Persistence of a positive swab beyond 24 h of life or positive IgM in the first 7 days of life are also considered [8].

One of the first communications and case reports with strong evidence pointing to transplacental virus passage was a case of a premature neonate (35.5 weeks) who was born with low 1- and 5-min' Apgar scores, with evidence of the E and S genes of SARS-CoV-2 in amniotic fluid, positive nasopharyngeal swabs, who on the third day of life developed neurological symptoms [9].

Provided vertical transmission occurs, it would be interesting to know which is the period of pregnancy that poses the greatest risk for the fetus and what consequences should be expected in the short or long term.

1.1.2. Immune activation

A second possible mechanism of neurodevelopmental compromise by SARS-CoV-2 is maternal immune activation (MIA) which may result in placental and fetal brain immune activation. This phenomenon has been previously reported following the epidemics of influenza, a virus that does not cross the placental barrier. In their review, Shook et al. describe that abnormal neurodevelopment in the offspring after influenza infection could include autism spectrum disorder, anxiety, schizophrenia and other serious neurological sequelae. Given the significant inflammatory and immune response in many COVID-19 cases, often including a proinflammatory cytokine storm, this mechanism of damage is plausible [3].

1.1.3. Maternal complications

Finally, an additional mechanism that could result in neurodevelopmental impairment is the occurrence of complications of pregnancy in SARS-CoV- 2 infected women. Placental dysfunction could result in intrauterine growth restriction, and infections themselves are associated with premature birth, both complications increasing risks in later development. Furthermore, during the pandemic, severe COVID-19 in the last trimester led to elective preterm delivery of pregnancy in many cases [3,10].

2. Neurodevelopment: follow up cohort studies

Several studies evaluated the influence of COVID-19 during pregnancy on later development [11–14]. Other publications discuss the possibility of neurodevelopmental changes in the offspring of infants born during the pandemic even in the absence of documented infection during pregnancy [15,16].

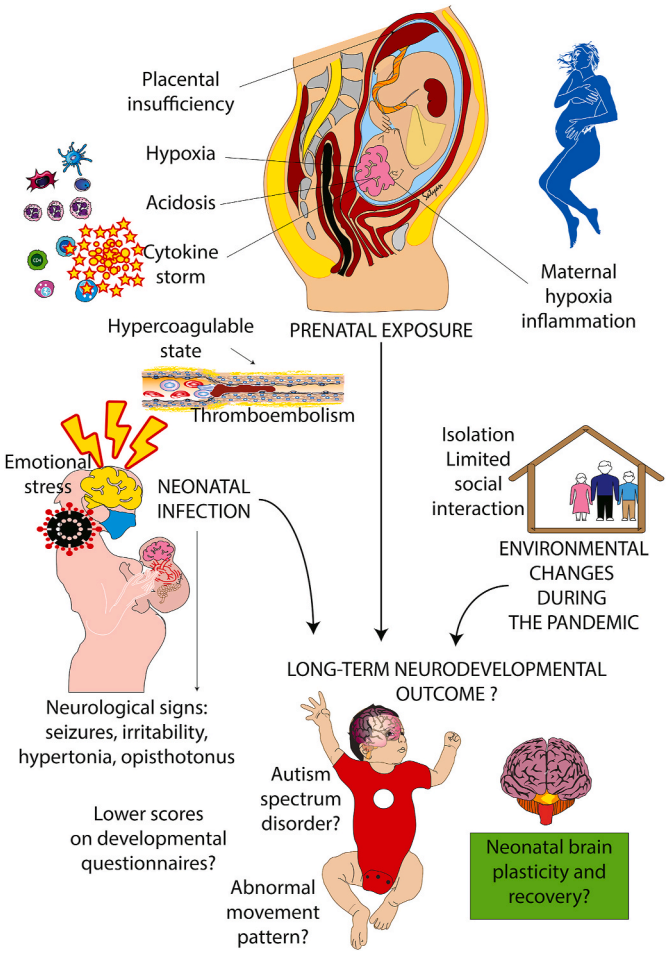

Fig. 1. Potential mechanisms for neurodevelopmental impairment of infants during the COVID-19 pandemic. Maternal infection and its consequences such as hypoxia, thromboembolism, inflammation and placental insufficiency can affect the fetal brain. Neonatal exposure and infection can rarely be associated with neurological involvement. The effect of environmental changes during the pandemic due to isolation, decreased interaction, parental stress etc., may also have contributed to neurodevelopmental changes. Although subtle impairment in various developmental scores is evident in studies, the plasticity of the neonatal brain might recover from these effects in a nurturing and supportive environment. Copyright Satyan Lakshminrusimha.

Edlow et al. reported data from 7772 infants born during 2020 at 6 hospitals in Massachusetts, including 222 whose mothers developed COVID-19 during pregnancy. Abnormal neurodevelopmental diagnoses at 12 months were more common in the offspring of infected mothers, particularly those exposed to third-trimester maternal infection (6.3 vs. 3.0%), even after adjusting for premature birth and several other variables. It is clear that additional neurodevelopmental effects may become apparent with longer follow-up [11].

In a cohort of 298 infants from Kuwait born to mothers with COVID-19 during pregnancy, using the Ages and Stages Questionnaire, 3rd edition (ASQ-3) at one year, 10% demonstrated developmental delay and this was more frequent when the infection occurred during the first and second trimester [12]. Similar findings were reported from a small cohort from Washington DC [13].

Aldrete Cortez et al. performed a small but elegant study: they videotaped 3-5 month-old infants for general movement assessment. They compared 28 infants born to mothers who developed SARS-CoV-2 infection in the third trimester with 28 unexposed controls. Infants in the exposed group had a 22% incidence of absent or decreased fidgety

movements, a finding that could be considered a potential early indicator of neurological dysfunction [14].

A study from New York evaluated 255 infants born in 2020 using the ASQ-3 at six months (114 in utero exposed to COVID-19 and 141 unexposed). They concluded that, compared to a historical pre-pandemic cohort, there was an increase in neurodevelopmental deficits in infants born during the pandemic which was not related to the exposure to SARS-CoV- 2 infection. However, the authors acknowledge that the results are self-perceived by the parents and that the ASQ-3 may have a modest correlation with future objective measures of neurodevelopment [15].

Similarly, Deoni and coworkers evaluated infants younger than 16 months using the Mullen Scales of Early Learning (MSEL). They compared 388 infants born before the pandemic to 137 born during the pandemic but with no history of SARS-CoV-2 infection. They found a decrease of nearly 30 points in cognitive performance which did not appear to be related to maternal stress [16].

More recently Bianco and coworkers reported a cohort of infants born in New York during the pandemic in whom changes in their temperament was found to be associated to maternal stress but not to SARS-CoV-2 infection during pregnancy [17].

Manning et al. performed MRIs at age three months on 75 infants born during the pandemic. They associated the findings of amygdala-prefrontal microstructural and functional connectivity measures to the degree of maternal anxiety and depression which was less prevalent when the mother had adequate social support [18]. Another small cohort study suggested that SARS-CoV-2 infection in pregnancy might affect auditory brain stem function [19].

3. SARS-CoV-2 prenatal and postnatal infections: neuroimaging findings

Although initially clinicians' impression was that prenatally and postnatally acquired neonatal infections with SARS-CoV-2 were mild, several reports demonstrated abnormal structural findings in the infants' brain. Lin et al. proposed several potential mechanisms for these effects: a direct impact of the virus, an immune or inflammatory processes, and some hypercoagulable states [20].

As mentioned before, Vivanti et al. communicated the case of a neonate with evidence suggesting vertical transmission. In the third postnatal day, the infant developed irritability, hypertonia and opisthotonos. CSF was sterile but with an initial inflammatory reaction. Brain MRI showed bilateral gliosis of the deep white periventricular and subcortical matter. The authors attribute the observed brain lesions to vascular inflammation induced by the viral infection [9]. A systematic review of 176 cases of neonatal COVID-19 by the same group of investigators reported 18% with neurological signs [21]. In a report of 5 cases of neonatal COVID-19 from China, MRI showed diverse abnormalities in four, partially correlated with decreased neurobehavioral scores [22].

We reported the case of a 17-day-old infant with a proven community-acquired SARS-CoV-2 infection who presented with seizures and subsequently developed hematological and cardiac compromise. Brain magnetic resonance showed two focal lesions in the white matter of the left frontal region, consistent with an ischemic focus. Viral PCR studies of CSF including SARS-CoV-2 were negative. At 2-year follow-up, neurodevelopment appeared normal [23]. Other authors reported cases of severe SARS-CoV-2 infections in neonates including seizures, other neurological signs and abnormal brain MRI [24–26].

In series of older infants and children with SARS-CoV-2 acquired infections, the reported incidence of neurological signs is variable. When those signs are present, abnormal findings in brain MRI are common [27]. The most frequently found brain imaging patterns include immune-mediated acute disseminated encephalomyelitis-like changes, myelitis, and neural enhancement [28].

3.1. Summary and conclusions

Following the declaration of the COVID-19 pandemic, those of us working in maternal, fetal, and neonatal medicine were worried about the impact of this new virus on mothers and infants. We were initially relieved when most newborns who had been exposed to COVID-19 appeared to be doing well [29].

Although controversy persists, most infants born to mothers who acquired SARS-CoV-2 during pregnancy are healthy and vertical transmission appears rare. Most neonates who develop COVID-19 have a mild course of the disease with unaffected outcomes. However, there are several reports of serious impact from SARS-CoV-2 on the neonatal brain of infected neonates.

Several follow-up studies strongly suggest that infants born during the pandemic have an increased frequency of neurodevelopmental and behavioral problems which, in general, appear independent from maternal infection during pregnancy and may be associated to with maternal stress.

According to Moyer, even if the brains of infants and young children are being affected, there are good chances for them to recover and catch up. Moyer said, "the brains of six-month-olds are very plastic, and we can get in there, and we can change their trajectory." [29] Although subtle to significant neurological findings are being reported in many studies, no clear pattern of neurodevelopmental impairment has been associated with prenatal or postnatal COVID-19 exposure or infection and long-term follow-up of these children is needed.

In order to disclose the real impact of perinatal-neonatal COVID-19 on the neurodevelopment of infants and children, collaborative studies with very long term follow-up will be necessary. The experience with previous respiratory virus pandemics demonstrated the appearance of psychologic, psychiatric, and developmental sequelae several years later [3]. This unfortunate history should be considered by healthcare authorities to acknowledge the need for supporting the organization and financing of programs that could give answers to many important questions.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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References

[1] 11 March WHO Director-General's opening remarks at the media briefings on COVID-19. 2020. Available at: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020. [Accessed 15 February 2023].
[2] Lukiw WJ, Pogue A, Hill JM. SARS-CoV-2 Infectivity and Neurological Targets in the brain. Cell Mol Neurobiol 2022;42(1):217–24.
[3] Shook LL, Sullivan EL, Lo JO, et al. COVID-19 in pregnancy: implications for fetal brain development. Trends Mol Med 2022;28(4):319–30.
[4] Alencar Ximenes RA, Miranda-Filho DB, Brickley EB, et al. Risk of adverse outcomes in offspring with RT-PCR confirmed prenatal Zika virus exposure: an individual participant data meta-analysis of 13 cohorts in the Zika Brazilian Cohorts Consortium. Lancet Reg Health Am. 2023;17:100395.
[5] Doneda C, Parazzini C, Righini A, et al. Early cerebral lesions in cytomegalovirus infection: prenatal MR imaging. Radiology 2010 May;255(2):613–21.
[6] World Health Organization. Definition and categorization of timing of mother-to-child transmission of SARS-CoV-2. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-mother-to-child-transmission-2021.1. [Accessed 16 February 2023].
[7] Shah PS, Diambomba Y, Acharya G, et al. Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetus and neonates. Acta Obstet Gynecol Scand 2020;99(5):565–8.
[8] Blumberg DA, Underwood MA, Hedriana H, Lakshminrusimha S. Vertical transmission of SARS-CoV-2: what is the optimal definition? Am J Perinatol 2020;37(8):769–72.

[9] Vivanti AJ, Vauloup-Fellous C, Prevot S, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun 2020;14;11(1):3572.
[10] Giuliani F, Oros D, Gunier RB, et al. Effects of prenatal exposure to maternal COVID-19 and perinatal care on neonatal outcome: results from the INTERCOVID Multinational Cohort Study. Am J Obstet Gynecol 2022 Sep;227(3):488.e1–488.e17.
[11] Edlow AG, Castro V, Shook LL, et al. Neurodevelopmental outcomes at 1 year infants o mothers who tested positive for SARS-CoV-2 during pregnancy. JAMA Netw Open 2022;5(6):e2215787.
[12] Ayed M, Embaireeg A, Kartam M, et al. Neurodevelopmental outcomes of infants born to mothers with SARS-CoV-2 infections during pregnancy: a national prospective study in Kuwait. BMC Pediatr 2022;22:319.
[13] Mulkey SB, Williams ME, Jadeed N, et al. Neurodevelopment in infants with antenatal or early neonatal exposure to SARS-CoV-2. Early Hum Dev 2022 Dec;175:105694.
[14] Aldrete-Cortez V, Bobadilla L, Tafoya SA, et al. Infants prenatally exposed to SARS-CoV-2 show the absence of fidgety movements and are at higher risk for neurological disorders: a comparative study. PLoS One 2022 May 4;17(5):e0267575.
[15] Shuffrey LC, Firestein MR, Kyle MH, et al. Association of birth during the COVID-19 pandemic with neurodevelopmental status at 6 Months in infants with and without in utero exposure to maternal SARS-CoV-2 infection. JAMA Pediatr 2022;176(6):e215563.
[16] Deoni SC, Beauchemin J, Volpe A, Dâ Sa V. RESONANCE consortium. The COVID-19 pandemic and early child cognitive development: a comparison of development in children born during the pandemic and historical references. medRxiv [Preprint] 2022 Aug 16;2021. 08.10.21261846.
[17] Bianco C, Sania A, Kyle MH, et al. Pandemic beyond the virus: maternal COVID-related postnatal stress is associated with infant temperament. Pediatr Res 2023;93(1):253–9.
[18] Manning KY, Long X, Watts D, et al. Prenatal maternal distress during the COVID-19 pandemic and associations with infant brain connectivity. Biol Psychiatr 2022;1;92(9):701–8.
[19] Veeranna SA, Youngblood PL, Bradshaw L, Marx CG. COVID-19 during pregnancy and its impact on the developing auditory system. Am J Otolaryngol 2022;43(4):103484.
[20] Lin JE, Asfour A, Sewell TB, et al. Neurological issues in children with COVID-19. Neurosci Lett 2021;743:135567.
[21] Raschetti R, Vivanti AJ, Vaulop-Fellous, et al. Synthesis and systematic review of reported neonatal SARS-CoV-2 infections. Nat Commun 2020;15;11(1):5164.
[22] Yan K, Xiao FF, Jiang YW, et al. Effects of SARS-CoV-2 infection on neuroimaging and neurobehaviour in neonates. World J Pediatr 2021;17:171–9.
[23] Brum AC, Glasman MP, De Luca MC, et al. Ischemic lesions in the brain of a neonate with SARS-CoV-2 infection. Pediatr Infect Dis J 2021;40(9):e340–3.
[24] Tetsuhara K, Akamine S, Matsubara Y, et al. Severe encephalopathy associated with SARS-CoV-2 Omicron BA.1 variant infection in a neonate. Brain Dev 2022;44(10):743–7.
[25] Alves L, Alcântara T, Hazin A, et al. White matter injury in a newborn infant with COVID-19: a case report. Neurol Clin Pract 2022;12(3):e22–4.
[26] Martin PJ, Felker M, Radhakrishnan R. MR imaging findings in a neonate with COVID -19-Associated encephalitis. Pediatr Neurol 2021 Jun;119:48–9.
[27] Rastogi S, Gala F, Kulkarni S, et al. Neurological and neuroradiological patterns with COVID-19 infection in children: a single institutional study. Indian J Radiol Imag 2022;32(4):510–22.
[28] Lindan CE, Mankad k, Ram D, et al. Neuroimaging manifestation in children with SARS-CoV-2 infection: a multinational, multicenter collaborative study. Lancet Child Adolesc Health 2021;5(3):167–77.
[29] Wenner Moyer M. The COVID generation: how is the pandemic affecting kids' brains? Nature 2022 Jan;601(7892):180–3.